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Original Scientific Paper

A NOVEL BIOMARKER TO PREDICT CONTRAST-INDUCED NEPHROPATHY AND THE REQUIREMENT FOR RENAL REPLACEMENT THERAPY IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY: C-PEPTIDE/HBA1C RATIO

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SUMMARY – Contrast-induced nephropathy (CIN) is a major cause of mortality and morbidity with an increasing incidence after coronary angiography (CAG). For this reason, it is important to identify subjects who are prone to CIN in advance and to take intensive protective measures accordingly. In this study, we aimed to reveal the role of C-peptide, HbA1c and C-peptide/HbA1c (CHR) ratio for predicting CIN development and the requirement for renal replacement therapy (RRT) in patients undergoing CAG. A total of 2,271 patients who underwent CAG between January 2019 and June 2021 were included in this prospective observational study. C-peptide and HbA1c levels were measured in all patients who underwent CAG, whether they were diabetic or not. We attempted to identify independent predictors for the development of CIN. In addition, patients who needed RRT after CIN were followed up for an average of 90 days. In a multivariate analysis, CHR was determined as an independent predictor of CIN and identified as an independent risk factor for the requirement for RRT in patients undergoing CAG. The main finding of our study was the fact that we identified CHR as an independent predictor for the development of CIN and the need for RRT in patients undergoing CAG.

Keywords: *Contrast-induced nephropathy; Coronary angiography; C-peptide; HbA1c; Renal replacement therapy*

Introduction

The incidence of contrast induced nephropathy (CIN) has become more prevalent with the increasingly frequent use of imaging methods that require contrast materials, such as tomography and angiography[1].

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Despite increasing preventive measures, CIN still remains a major cause of mortality and morbidity, and continues to be one of the leading causes of in-hospital acute renal failure[2]. Both the growing elderly population and the increasing incidence of comorbidities that predispose to the development of CIN, such as diabetes mellitus (DM), have made it necessary to predict the risk of CIN in this particularly susceptible group of patients and to implement more intensive protective measures against it[3]. Although the underlying mechanism is not clear, renal medullary hypoxia, direct tubular toxicity, oxidant-antioxidant imbalance, vasoconstrictor-vasorelaxant imbalance, apoptosis, immune/inflammation and epigenetic regulation are blamed in CIN[4]. To date, there is no treatment that can completely prevent CIN, therefore risk estimation and effective preventive strategies in vulnerable patients play a key role in reducing the occurrence of CIN[5]. After the development of contrast-mediated acute renal failure, treatments are limited. Renal replacement therapy (RRT) remains the only option in cases where radiocontrast media cause severe insufficiency and conventional treatments such as hydration are insufficient[6].

It is known that DM patients are much more prone to developing CIN[7]. CIN has become a significant morbidity and an important cause of mortality in this patient group, due to both the increased incidence of cardiovascular disease and the correspondingly more frequent use of radiocontrast imaging, as well as these patients' inherent predisposition to radiocontrast nephropathy[8]. Therefore, predicting the development of CIN in this patient group — in whom mortality and morbidity rates are inherently higher due to underlying comorbidities such as diabetes — and implementing preventive measures against CIN itself play a key role in their clinical management. Identifying low-cost biomarker tools that can be easily calculated from routine bedside blood analyses in this patient group may help to overcome the handicap present in this area.

C-peptide is a molecule that is produced in the same amounts as insulin and is an indicator of endogenous insulin secretion. It is used in clinical practice to differentiate between Type 1 and Type 2 diabetes and to regulate treatment modalities accordingly[9]. C-peptide, which was previously thought to be a biologically inert molecule, has been found to be an important nephroprotective and vasculoprotective molecule in clinical studies[10,11]. HbA1c is the glycosylated hemoglobin fraction that represents an individual's blood sugar regulation over the three months leading to testing[12]. It has been observed that high HbA1c values are associated with increased microvascular complications like nephropathy in DM patients[13]. It has also been found that high HbA1c levels are associated with an increased incidence of contrast nephropathy[14]. Therefore, combining the renoprotective properties of C-peptide and HbA1c, which is associated with microvascular complications, in a single fraction may be a useful tool to predict the development of CIN and the need for RRT. Therefore, in this study, we aimed to investigate the role of the C-peptide/HbA1c ratio (CHR) in predicting CIN and the requirement for RRT in diabetic and non-diabetic patients who underwent CAG. As far as we know, there is no study in the literature showing the effects of the C-peptide/HbA1c ratio in CIN and RRT requirement.

Methods

Trial Design and Study Population

The study was designed as a single-center, prospective, cohort and unblinded study. A total of 2,271 patients who underwent CAG because of acute coronary syndrome (ACS) and stable angina pectoris (SAP) between January 2019 and June 2021 were included. The patients were divided into groups according to CAG indication and whether they were diabetic or not (Figure 1A). Patients who developed CIN were followed for 90 days to determine the need for RRT (Figure 1B). Overall survival at day 90 was considered the primary outcome. Diagnosis and treatment were performed according to current guidelines. Exclusion criteria were as follows: active hepatitis, active infection, chronic renal disease (GFR < 15 mL/min or hemodialysis treatment), serious laboratory and clinical abnormalities (a blood urea nitrogen greater than 100 mg/dl, serum potassium concentration greater than 6 mmol/L, pH below 7.15, Killip class IV, cardiac arrest), history of cancer, cases given more than 4 ml/kg of contrast agent, using statin-derived antilipidemic drugs, undergoing radial access, Type 1 diabetes,

receiving contrast agent for imaging in the previous 2 weeks, Coronary Artery Bypass Grafting (CABG). The study was approved by the Ethics Committee of our hospital and was performed in accordance with the rules of the Declaration of Helsinki.

Study Protocols and Definitions

Patients who underwent CAG with a prediagnosis of ACS or SAP were divided into 2 groups according to the development of CIN; those who did not develop CIN (group 1) and those who developed CIN (group 2). Basal blood samples were routinely taken from the patients at the time of admission and 72 hours after the invasive procedure. In addition, fasting glucose, C-peptide and HbA1c levels were measured for all patients.

Diabetes is defined according to the following criteria (1): fasting plasma glucose (FPG) > 126 mg/dL (7.0 mmol/L) (2); 2 h plasma glucose (PG) > 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT) (3); HbA1c > 6.5% (48 mmol/mol) (4); and a random plasma glucose > 200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. CIN is defined as an increase in serum creatinine of ≥ 0.5 mg/dL or ≥ 25% from baseline, assessed within 48–72 hours after the administration of a contrast medium (CM)[1]. A stenosis of ≥ 50% of at least one epicardial coronary artery was defined as coronary artery disease (CAD), and the severity of CAD was assessed by the number of stenoses of ≥ 50% of the epicardial coronary arteries.

Estimated glomerular filtration rate (e-GFR) was calculated with the formula: 75 (ml min^{-1} per 1.73 m^2) = 186 × (serum creatinine(SCr)) -1.154 × (age) – 0.0203 (0.742 if female) × (1.210 if black). RRT was performed according to current diagnosis and treatment guidelines. If there was a requirement for RRT after 3 months, it was accepted as permanent dialysis.

All patients underwent CAG using the classical Judkins technique via the standard femoral route. Patients were hydrated with 0.9% saline at 1 mL/kg/hr for 24 hours before and after CAG. Hourly hydration amounts were halved in patients with acute heart failure. A nonionic, low-osmolality, iodinated CM (Iohexol-Omnipaque®) was used as a standard for angiographic imaging in our clinic. Maximal contrast agent usage was limited to 4 mL/kg. We investigated the predictive value of CIN development by comparing the C-peptide, HbA1c and CHR ratios of the patients. Also, patients were compared in terms of the development of CIN according to the indications of CAG (ST-elevation myocardial infarction [STEMI], unstable angina pectoris [UAP], stable angina pectoris [SAP] and non-ST-elevation myocardial infarction [NSTEMI]). Additionally, they were divided into quartiles according to their CHR values and the incidence of CIN development according to the quartiles was compared. The patients who developed CIN were also divided into groups according to their need for RRT and their 90-day survival rates were compared. All methods were carried out in accordance with relevant guidelines and regulations.

Statistical analysis

Statistical Program for Social Sciences 20 (IBM SPSS, Chicago, IL, USA) was used for all statistical calculations. The Kolmogorov-Smirnov test was used to determine whether the data fit the normal distribution. Continuous variables that fit the normal distribution were expressed as means ± standard deviation (SD), and those that did not fit the normal distribution were expressed as a median with interquartile range (IQR). Comparisons between CIN groups were analyzed using the Mann-Whitney U test or independent t-test, where appropriate. The Chi-square test was applied to categorical variables. Pearson's correlation coefficient was used to determine the relationship between CHR and other continuous variables. Univariate and multivariate regression analyses were performed to determine the independent predictors of CIN. Baseline variables with statistical significance ($P < 0.01$) according to the univariate analysis were included in the multivariate logistic regression analysis. Predictive validities were quantified as the Area under the ROC curve (c statistics), and these comparisons were done using MedCalc 16 statistical software. Cumulative overall and event-free survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Two-tailed *P*-values of < 0.05 were considered to be statistically significant.

Results

A total of 2,271 patients who underwent CAG were included in this study, 64.7% of which were male. The baseline clinical and demographic characteristics of the patients are shown in Table 1. The mean age of the study population was 59.93 years. According to the developmental status of CIN, the patients were divided into two groups: those who did not develop CIN (group 1) and those who did (group 2) (Table1). CAG was performed in 1,153 patients (65.6%) with NSTEMI/UAP, 699 patients (30.7%) with STEMI and 419 patients (18.4%) with SAP. CIN developed in 23.1% of NSTEMI/UAP patients, 29.8% of STEMI patients and 9.5% of SAP patients (Figure 1). The incidence of developing CIN was statistically more significant in STEMI patients than in NSTEMI/UAP and SAP patients, and in NSTEMI/UAP patients than in SAP patients ($P < 0.001$, for all). As seen in Table 1, CIN development in advanced age, patients with DM, hyperlipidemia, severe CAD, those with low left ventricular ejection fraction (LVEF), hemoglobin, hematocrit, albumin, initial creatinine, C-peptide and CHR and in patients with high serum HbA1c, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride levels were statistically more significant ($P < 0.05$, for all). In correlation analysis, CHR was negatively correlated with the severity of CAD ($r = -0.154$, $P < 0.001$) and positively correlated with high density lipoprotein-cholesterol (HDL-C) and estimated glomerular filtration rate (e-GFR) ($r = 0.170$, $P < 0.001$; $r = 0.044$, $P = 0.036$; respectively) (Table 2). Age, DM, STEMI, initial creatinine and the severity of CAD and CHR were found to be independent predictors of CIN development in a multivariate binary logistic regression analysis (OR 1.021, 95%

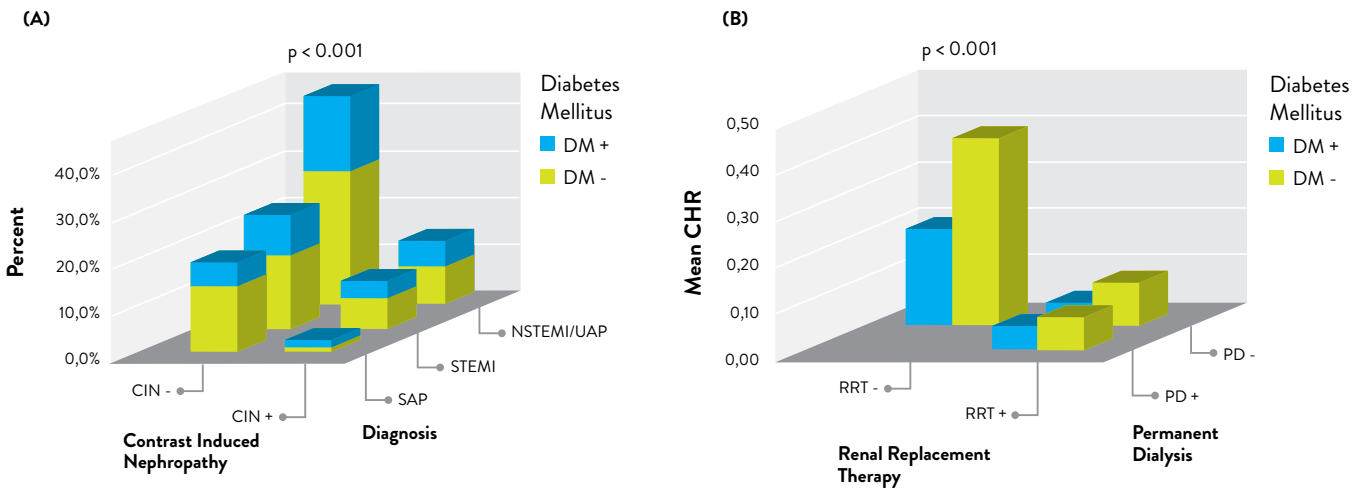


Figure 1. 1A. Contrast-induced nephropathy rates according to diabetes mellitus and diagnosis types in patients who underwent coronary angiography (CIN- refers to the group that did not develop contrast induced nephropathy, while CIN+ refers to the group that developed nephropathy.); 1B. Diabetic status and permanent dialysis rates of patients receiving renal replacement therapy according to mean CHR values.(RRT-:…) patients who did not receive renal replacement therapy, RRT+: patients who received renal replacement therapy; PD+: indicates patients who needed permanent dialysis, PD-: indicates patients who do not.)

CIN: contrast induced nephropathy; CHR: C-peptide /HbA1c ratio; DM: diabetes mellitus; UAP: unstable angina pectoris; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; SAP: stable angina pectoris; RRT: renal replacement therapy; PD: permanent dialysis

Table 1. Distribution of clinical and demographic patient characteristics according to the development of contrast-induced nephropathy

Variables		**Total (n=2271)**	**Group 1 (CIN-) (n=1755)**	**Group 2 (CIN+) (n=516)**	***P*-value**
Demographics and medical history	Age, years	59.93 (51-68)	59 (51-67)	63 (54-72)	<0.001
	Sex, male, (%)	1471 (64.7)	1150 (65.5)	321 (62.2)	0.272
	BMI, Kg/m^2	26.1 ± 2.94	25.08 ± 3.10	25.83 ± 3.23	0.455
	Diabetes mellitus, (%)	796 (35)	592 (33.7)	204 (39.5)	0.015
	Hypertension, (%)	1509 (66.4)	1148 (65.4)	361 (69.9)	0.054
	Hyperlipidemia, (%)	1808 (79.6)	1348 (76.8)	460 (89.1)	<0.001
	Smoking, (%)	1326 (58.3)	1032 (58.8)	294 (56.9)	0.459
Diagnosis, n (%)	NSTEMI/UAP	1153 (65.6)	886 (50.4)	267 (51.7)	<0.001
	STEMI	699 (30.7)	490 (27.9)	209 (40.5)	
	SAP	419 (18.4)	379 (21.5)	40 (7.7)	
Laboratory Results	FPG, (mg/dL)	149.74 (99.0-172.0)	120 (98.0-170.0)	123 (101-178.0)	0.037
	Initial creatinine, (mg/dL)	0.89 (0.70-1.00)	0.80 (0.70-1.00)	0.64 (0.78-0.90)	<0.001
	Third day creatinine, (mg/dL)	1.03 (0.78-1.00)	0.8 (0.7-1.0)	1.0 (0.90-1.20)	<0.001
	Uric acid, (mg/dL)	5.29 (4.20-6.10)	5.20 (4.20-6.10)	5.0 (4.10-6.00)	0.187
	Albumin, (mg/dL)	4.32 (3.90-4.50)	4.30 (4.00-4.50)	4.10 (3.90-4.40)	<0.001
	Triglycerides, (mg/dL)	218.6 (101.0-215.0)	142.0 (101.0-201.0.)	151 (106.0-278.0)	<0.001
	TC, (mg/dL)	220.6 (145.0-209.0)	178(144.0-205.0)	182.0(153.0-226.0)	0.002
	HDL-C, (mg/dL)	36.3(29.7-41.0)	35.0 (30.0-41.0)	33 (27.0-38.0)	<0.001
	LDL-C, (mg/dL)	108.8 (82.0-132.0)	105.0 (81.0-130.0)	111.0 (86.0-137.0)	0.001
	CRP, (mg/dL)	2.03 (0.2-1.2)	0.52 (0.20-1.18)	0.58 (0.21-1.26)	0.254
	e-GFR, (mL/min)	88.6 (77.0-102.0)	93.0 (76.0-102.0)	93.0 (80.0-102.0)	0.520
	WBC, (x1000/mm3)	10.45 (7.60-12.38)	9.48(7.60-12.10)	10.03 (7.65-12.75)	0.033
	Lymphocyte, (x1000/mm3)	2.23 (1.47-2.63)	2.00 (1.47-2.60)	2.00 (1.43-2.70)	0.956
	Monocytes, (x1000/mm3)	0.65 (0.45-0.80)	0.60 (0.46-0.81)	0.60 (0.44-0.80)	0.303
	Neutrophil, (x1000/mm3)	7.17 (4.50-9.00)	6.30 (4.50-8.80)	6.70 (4.60-9.85)	0.026
	RDW, fL	15.97 (12.00-13.60)	12.7 (12.0-13.5)	12.9 (12.2-13.7)	0.39
	MPV, fL	9.52 (7.23-8.81)	7.97 (7.20-8.80)	8.08 (7.40-8.85)	0.130
	LDH, U/L	305.7 (210.0-329.0)	250.0 (210.0-323.5)	256.0 (214.0-331.0)	0.246
	Hemoglobin, (mg/dL)	14.1 (12.8-15.0)	14.0 (13.0-15.0)	13.4 (12.0-15.0)	<0.001
	Hematocrit, (%)	42.9 (39.0-47.0)	43.0 (40.0-47.0)	42.0 (37.0-46.0)	<0.001
	Platelet count, (x1000/mm3)	267.6 (216.8-308.2)	259.0 (215.0-309.0)	257.0 (223.0-308.0)	0.725
	ΔCr, (%)	0.18 (0.00-0.20)	0.0 (0.00-0.12)	0.33 (0.27-0.44)	<0.001
	Hemoglobin A1c, (%)	6.02 (5.30-6.50)	5.90 (5.10-6.50)	6.00 (5.40-8.20)	<0.001
	C-peptide, (mg/dL)	3.26 (1.40-4.60)	3.09 (1.44-4.80)	1.70 (1.00-2.68)	<0.001
	CHR	0.34 (0.21-0.81)	0.35 (0.21.-0.75)	0.20 (0.18-0.33)	<0.001
Angiographic, echocardiographic and other parameters	Amount of contrast agent, (ml)	139.5 (90.0-200.0)	100.0 (85.0-200.0)	100.0 (90.0-180.0)	0.762
	Severity of CAD	1.69 (1.0-3.0)	2.0 (1.0-2.0)	2 (1.0->2.0)	<0.001
	LVEF, (%)	53.3 (51.0-62.0)	51.0 (46.0-55.0)	45 (41.0-52.0)	0.023
	PCI applied, (%)	1982 (87.2)	1530 (87.1)	452 (87.5)	0.802
	RRT, (%)	31 (0.01)	0 (0.0)	31 (0.06)	<0.001

Data presented as mean ± SD/IQR or number (%) of the patients

Abbreviations: BMI: body mass index; CAD: coronary artery disease; CRP: C-reactive protein; CHR: C-peptide/HbA1c ratio; CIN: contrast induced nephropathy; ΔCr: creatinine increase rate; FPG: Fasting plasma glucose; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; UAP: unstable angina pectoris; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; SAP: stable angina pectoris; PCI: percutaneous coronary intervention; eGFR: estimated glomerular filtration rate; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MPV: mean platelet volume; RDW: red cell distribution width; RRT: renal replacement therapy; WBC: White blood cell

Table 2. Correlation analysis between CHR and other clinical parameters

Variables	Correlation coefficient (r)	*P*-value
Severity of CAD	-0.154	<0.001
HDL-C, (mg/dL)	0.170	0.001
e-GFR, (mL/min)	0.044	0.036

CAD: coronary artery disease; CHR: C-peptide/HbA1c ratio; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol

CI 1.011–1.031, $P<0.001$; OR 0.748, 95% CI 0.584–0.959, $P=0.022$; OR 1.955, 95% CI 1.282–2.981, $P=0.002$; OR 0.250, 95% CI 0.155–0.406, $P<0.001$; OR 1.421, 95% CI 1.253–1.611, $P<0.001$; OR 0.083, 95% CI 0.050–0.137, respectively) (Table 3). We compared the CHR levels of patients with and without CIN. As seen in Figure 2A, the incidence of CIN was significantly higher in the group with low CHR levels than in the group with high CHR levels ($P<0.001$). Afterwards, we divided the patients into 4 groups according to their CHR quartiles (Q) (Q1[CHR ≤ 0.21], Q2[0.21 < CHR ≤ 0.49], Q3[0.49 < CHR ≤ 0.68], Q4[CHR > 0.68]) and investigated the incidence of CIN according to the quartiles. As seen in Figure 2B, the incidence of CIN in the quartiles was 50.1%, 20.3%, 12.9% and 7.4%, respectively, and it was statistically significant ($P<0.001$). When a Receiver Operating Characteristic (ROC) curve analysis was performed, the optimal cut-off value of CHR for predicting CIN was determined to be < 0.21, which was predictive of CIN with 86% sensitivity and 65% specificity (area under the curve: 0.734, 95% confidence interval [CI]: 0.715–0.752, $P<0.001$) (Figure 3A). In addition, the ROC curves were compared to determine whether there was an additional benefit of using CHR on C-peptide and HbA1c. It was found that the Area Under the Curve (AUC) of CHR was significantly higher than both the AUC of C-peptide (0.734 vs 0.678, $P<0.001$) and HbA1C (0.734 vs 0.579, $P<0.001$) for predicting CIN (Figure 3A). In addition, patients were divided into diabetic and non-diabetic patients, and the ROC curve analyses were performed separately, while CHR, C-peptide and HbA1c were compared in pairs to predict CIN (Figure 3B-C). Although CHR was statistically more

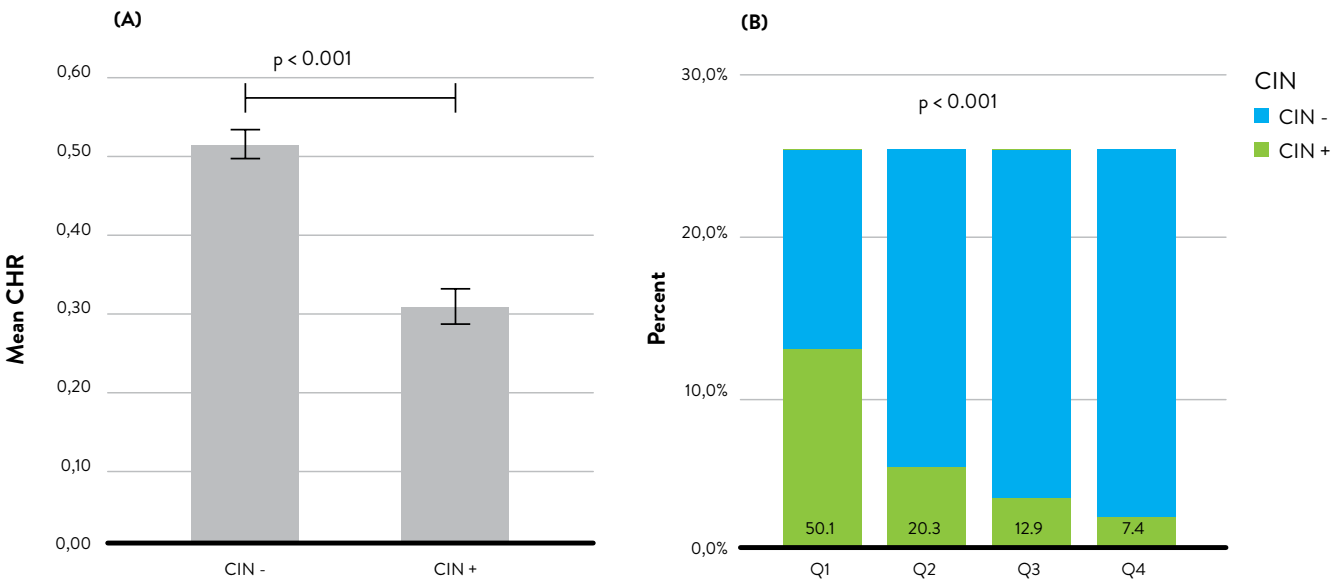


Figure 2. Comparison in the level of CHR between CIN- and CIN+ group (A), and the incidence of CIN according to the quartiles (Q) of CHR (B). CIN: Contrast induced nephropathy; CHR: C-peptide/HbA1c ratio.

Table 3. Univariate and multivariate logistic regression analysis of CIN

Variable	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age	1.025 (1.016-1.033)	<0.001	1.021 (1.011-1.031)	<0.001
Diabetes Mellitus	1.284 (1.049-1.573)	0.015	0.748 (0.584-0.959)	0.022
Hyperlipidemia	2.480 (1.840-3.344)	<0.001	0.984 (0.678-1.427)	0.931
Diagnosis (STEMI/UAP/ NSTEMI/SAP)	2.885 (2.005-4.066)	<0.001	1.955 (1.282-2.981)	0.002
İnitial creatinine, (mg/dL)	0.390 (0.255-1.598)	<0.001	0.250 (0.155-0.406)	<0.001
HDL-C, (mg/dL)	1.028 (1.004-0.1052)	0.020	0.991 (0.982-1.001)	0.670
LDL-C, (mg/dL)	1.004 (1.002-1.007)	0.001	1.003 (1.000-1.006)	0.310
Hematocrit, %	0.980 (0.966-0.994)	0.006	1.017 (0.990-1.044)	0.216
Hemoglobin, (mg/dL)	0.946 (0.905-0.988)	0.013	0.975 (0.939-1.012)	0.186
Severity of CAD	1.622 (1.466-1.795)	<0.001	1.421 (1.253-1.611)	<0.001
C- peptide, (mg/dL)	0.771 (0.728-0.816)	<0.001	1.007 (0.936-1.083)	0.056
HbA1c, (mg/dL)	1.259 (1.194-1.329)	<0.001	1.207 (1.133-1.286)	0.581
CHR	0.065 (0.040-0.104)	<0.001	0.083 (0.050-0.137)	<0.001

CAD: coronary artery disease; CHR: C-peptide/HbA1c ratio; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: Hemoglobin A1c; UAP: unstable angina pectoris; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; SAP: stable angina pectoris

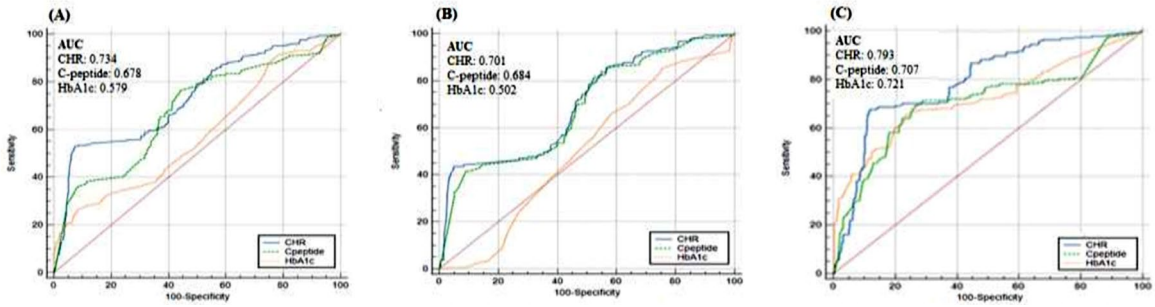
Table 4. Distribution of baseline clinical and demographic characteristics of patients with contrast-induced nephropathy according to the requirement for renal replacement therapy

Variables		**Overall CIN+ (n=516)**	**Without RRT (n=485)**	**With RRT (n=31)**	***P*-value**
Demographics and medical history	Age, years	63 (54-72)	63 (53-71)	62 (60-73)	0.002
	Sex, male, (%)	321 (62.2)	307 (63.2)	14 (45.1)	0.043
	BMI, Kg/m^2	26.5 ± 2,90	25.10 ± 3.20	25.45 ± 3.03	0.324
	Diabetes mellitus, (%)	198 (38.3)	178 (36.7)	20 (64.5)	0.002
	Hypertension, (%)	361 (22.5)	325 (67.0)	26 (83.8)	0.081
	SBP (mmHg)	120.07 ± 16.05	122.88 ± 15.60	120.59 ± 16.44	0.093
	DBP (mmHg)	76.21 ± 10.78	78.80 ± 10.64	77.20 ± 10.91	0.124
	Hyperlipidemia, (%)	460 (89.1)	432 (89.0)	28 (90.3)	0.828
	Smoking, (%)	294 (56.9)	283 (58.3)	11 (35.4)	0.013
Diagnosis, n (%)	NSTEMI/UAP	267 (51.7)	245 (50.5)	22 (70.9)	0.080
	STEMI	209 (40.5)	202 (41.6)	7 (22.5)	
	SAP	40 (0.077)	38 (0.078)	2 (0.064)	

Table 4. Continued

Laboratory Results	FPG, (mg/dL)	225.2 ± 101.3	143.5 ± 62.6	225.2 ± 101.3	<0.001
	Initial creatinine, (mg/dL)	0.78 (0.64-0.90)	0.78 (0.61-0.90)	1.10 (1.00-1.40)	<0.001
	Third day creatinine, (mg/dL)	1.00 (0.90-1.20)	1.00 (0.90-1.20)	1.60 (1.40-2.10)	<0.001
	Third day Urea (mg/dL)	47.3 (35.1-59.8)	44.1 (34.8–53.5)	63.9 (56.2–78.9)	<0.001
	Uric acid, (mg/dL)	5.00 (4.10-6.00)	5.00 (4.20-6.00)	4.3 (3.50-6.00)	0.041
	Albumin, (mg/dL)	3.95 ± 0.30	4.07 ± 0.46	3.95 ± 0.30	0.187
	Triglycerides, (mg/dL)	151.0 (106.0-278.0)	149.0 (101.0-272.7)	254.0 (140.0-289.0)	0.001
	TC, (mg/dL)	197.1 ± 53.7	188.1 ± 53.8	197.1 ± 53.7	0.402
	HDL-C, (mg/dL)	30.08 ± 9.32	35.45 ± 19.01	30.08 ± 9.32	0.141
	LDL-C, (mg/dL)	115.27 ± 41.95	115.97 ± 38.08	115.27 ± 41.95	0.927
	CRP, (mg/dL)	0.58 (0.21-1.26)	0.56 (0.20-1.20)	1.01 (0.30-3.18)	0.032
	e-GFR, (mL/min)	93 (80.0-102.0)	93.0 (80.0-103.0)	75.0 (45.0.-80.0)	0.018
	WBC, (x1000/mm3)	11.19 ± 3.88	10.73 ± 4.27	11.19 ± 3.88	0.525
	Lymphocyte, (x1000/mm3)	2.45 ± 1.19	2.26 ± 1.69	2.45 ± 1.19	0.257
	Monocytes, (x1000/mm3)	0.68 ± 0.42	0.99 ± 1.81	0.68 ± 0.42	0.045
	Neutrophil, (x1000/mm3)	6.7 (4.60-9.85)	6.60 (4.60-9.80)	8.10 (4.50-10.40)	0.208
	RDW, fL	13.18 ± 1.21	13.29 ± 6.14	13.18 ± 1.21	0.822
	MPV, fL	8.13 ± 0.97	8.27 ± 1.71	8.13 ± 0.97	0.513
	LDH, U/L	250.5 (210.0-329.0)	250.0 (210.0-326.0)	281.0 (238.0-362.0)	0.142
	Hemoglobin, (mg/dL)	13.53 ± 1.88	13.59 ± 2.01	13.53 ± 1.88	0.894
	Hematocrit, (%)	42.0 (37.0-46.0)	42.0 (37.0-46.0)	40.5 (37.1-47.3)	0.140
	Platelet count, (x1000/mm3)	285.7 ± 75.8	276.8 ± 92.7	285.7 ± 75.8	0.546
	ΔCr, (%)	0.33(0.27-0.44)	0.33 (0.27-0.42)	0.33 (0.28-0.70)	<0.001
	Hemoglobin A1c, (mg/dL)	5.90 (5.30-6.80)	5.80 (5.35-6.55)	6.90 (4.00-8.60)	0.001
	C-peptide, (mg/dL)	1.70 (1.00-2.50)	1.70 (1.02-2.59)	1.00 (0.72-2.10)	0.003
	CHR	0.09 ± 0.02	0.33 ± 0.23	0.09 ± 0.02	0.001
Angiographic, echocardiographic and other parameters	Amount of contrast agent, (ml)	150 (120.0-200.0)	140.0 (90.0-200.0)	150.0 (100.0-200.0)	0.067
	Severity of CAD	2.0 (1.0-3.0)	2.0 (1.0->2.0)	2 (2.0->2.0)	0.066
	LVEF, (%)	48.0 (41.0-51.0)	47.0 (46.0-55.0)	45 (41.0-52.0)	0.080
	PCI applied, (%)	452 (87.5)	425 (87.6)	27 (87.0)	0.931
	Chronic Kidney Disease, (%)	75 (14.5)	59 (12.1)	16 (51.6)	<0.001
	Length of CICU stay, (days)	9 (5–15)	8 (3–14)	13 (7–21)	<0.001
	APACHE II score	18 (12-21)	16 (14–23)	27 (24–30)	0.001
	90-day total mortality, (%)	71 (13.7)	58 (11.9)	13 (41.9)	<0.001
	CICU mortality, (%)	36 (6.9)	25 (5.1)	11 (35.4)	<0.001
	Permanent Dialysis (Dialysis need after 3 months), (%)	5 (0.009)	0 (00.0)	5 (16.1)	<0.001

Data presented as mean ± SD/IQR or number (%) of the patients
BMI: body mass index; CAD: coronary artery disease; CICU: coronary intensive care unit; CRP: C-reactive protein; CHR: C-peptide/HbA1c ratio; CIN: contrast induced nephropathy; ΔCr: creatinine increase rate; FPG: Fasting plasma glucose; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; UAP: unstable angina pectoris; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; SAP: stable angina pectoris; PCI: percutaneous coronary intervention; eGFR: estimated glomerular filtration rate; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MPV: mean platelet volume; RDW: red cell distribution width; RRT: renal replacement therapy; WBC: White blood cell



Pairwise comparison of ROC curves of all patients

Variables	ΔAUC	95%CI	*P*-value
CHR-C-peptide	0.016	0.0314-0.0806	P<0.0001
CHR-HbAlc	0.186	0.118-0.192	P<0.0001
C-peptide-HbAlc	0.170	0.589-0.139	P<0.0001

Pairwise comparison of ROC curves of non-diabetic patients

Variables	ΔAUC	95%CI	*P*-value
CHR-C-peptide	0.0168	0.0058-0.0277	P<0.0026
CHR-HbAlc	0.199	0.1490-0.2480	P<0.0001
C-peptide-HbAlc	0.182	0.1350-0.2290	P<0.0001

Pairwise comparison of ROC curves of non-diabetic patients

Variables	ΔAUC	95%CI	*P*-value
CHR-C-peptide	0.0852	0.0340-0.1360	P<0.0011
CHR-HbAlc	0.0717	0.0088-0.1340	P<0.0253
C-peptide-HbAlc	0.0135	0.0463-0.0732	P<0.6583

Figure 3. Pairwise comparison of ROC curves of C peptide, HbA1c, and CHR in all patients (A), non-diabetics (B), and diabetics (C)

Table 5. Univariate and multivariate logistic regression analysis of RRT requirement

Variable	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age	1.031 (0.998-1.064)	0.063		
Sex	0.477 (0.230-0.992)	0.047	0.569 (0.255-1.269)	0.168
Diabetes Mellitus	2.388 (1.143-4.990)	0.021	0.905 (0.332-2.466)	0.845
Diagnosis (STEMI/UAP/NSTEMI)	1.706 (0.386-7.550)	0.093		
İnitial creatinine, (mg/dL)	1.718 (0.763-3.870)	0.191		
Severity of CAD	1.845 (1.140-2.986)	0.013	1.604 (0.975-2.639)	0.063
Chronic Kidney Disease, (%)	0.203 (0.095-0.435)	*P*<0.001	0.212 (0.065-0.695)	0.010
Amount of contrast agent, (ml)	1.007 (1.001-1.013)	0.018	1.004 (0.997-1.012)	0.261
C- peptide, (mg/dL)	0.569 (0.360-0.901)	0.016	0.582 (0.293-1.158)	0.123
HbA1c, (mg/dL)	0.778 (0.617-0.980)	0.033	0.926 (0.757-1.131)	0.450
CHR	0.001 (0.000-0.047)	0.001	0.001 (0.000-0.067)	0.001

CAD: coronary artery disease; CHR: C-peptide/HbA1c ratio; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein-C; HbA1c: Hemoglobin A1c; UAP: unstable angina pectoris; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; SAP: stable angina pectoris

significant in predicting CIN than C-peptide and HbA1c in both diabetic and non-diabetic patients, this significance should have been greater in diabetic patients than in non-diabetic patients (AUC: 0.793, 95% confidence interval [CI]: 0.763–0.820 vs AUC: 0.701, 95% confidence interval [CI]: 0.677–0.724; $P < 0.001$, respectively). A total of 6% of the patients who developed CIN required RRT. Patients who required RRT and those who did not were compared according to their baseline demographic and clinical characteristics (Table 4). Advanced age, female sex, DM and smoking status were statistically significant in terms of RRT

requirement (< 0.05 for all). Increased fasting plasma glucose (FPG), triglyceride, C-reactive protein (CRP), HbA1c levels and low initial creatinine, uric acid, GFR, C-peptide, CHR levels were also statistically significant for RRT requirement (< 0.05 for all). Those who needed RRT had a significantly higher APACHE II score. While 90-day total mortality was 49.1% in patients who needed RRT, this rate was 11.9% in patients who did not. In addition, patients who received RRT had higher ICU mortality than those who did not, and those with chronic kidney disease (CKD) had a significantly higher requirement for RRT ($P < 0.001$; $P < 0.001$, respectively). The need for permanent dialysis after 3 months of RRT was 16.1%. DM status, RRT requirement and permanent dialysis status as a result of 90-day follow-up were compared according to mean CHR values of patients who developed CIN (Figure 1B). Mean CHR values were lower in patients who needed RRT ($P < 0.001$). Also, patients who received RRT were more likely to be diabetic ($P = 0.002$) and those who needed permanent dialysis had lower mean CHR values ($P = 0.027$). In a multivariate regression analysis, CKD and CHR were determined as independent risk factors for RRT requirement (OR 0.212, 95% CI 0.065–0.695, $P = 0.010$; OR 0.001, 95% CI 0.000–0.067, $P = 0.001$, respectively) (Table 5). The Kaplan-Meier analysis showed that there was a significantly higher incidence of overall mortality in patients who received RRT than in those who did not ($P < 0.001$) (Figure 4).

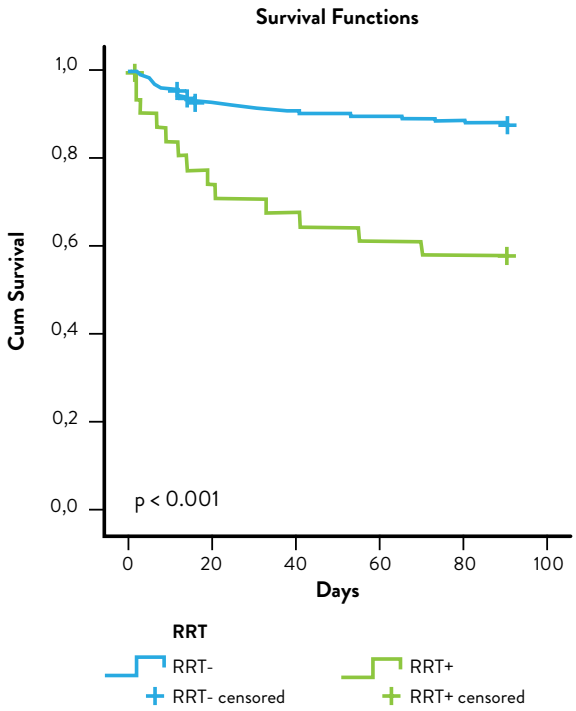


Figure 4. Kaplan Meier plot. The Kaplan-Meier plot estimate of overall mortality at day 90 in patients who developed CIN was 41.9% (95% confidence interval [CI], 48.8 to 74.2) in those receiving renal replacement therapy and 11.9% (95% confidence interval [CI], 80.1 to 84.2) in those who did not. The survival of patients who required RRT was significantly lower than of the patients who did not receive RRT (P < 0.001, log-rank test). RRT: renal replacement therapy

Discussion

One of the major findings of our study was the fact that combining C-peptide and HbA1c in a single fraction predicts the development of CIN better than using them separately in patients undergoing CAG, more specifically in DM patients, and that CHR is an independent predictor of RRT requirement. In addition, the need for RRT in patients who develop CIN significantly increases the 90-day total mortality.

DM is one of the major predisposing factors for the development of CIN[15]. The pathophysiology of the effect of radiocontrast agents on the kidneys is complex and multiple mechanisms have been implicated. Renal hypoxia and the generation of reactive oxygen species (ROS) play a key role in the development of CIN, and these pathophysiological processes are more pronounced in diabetic kidneys[16]. Some of the prominent consequences of these mechanisms are impaired tubular transport activity, increased oxygen consumption and production of reactive oxygen species, impaired vascular tone and peritubular blood flow, impaired NO-mediated vasodilation, increased susceptibility to endothelin and adenosine-related vasoconstriction[17-20]. In addition, micro and macrovascular effects and tubulointerstitial damage in the diabetic kidney impair renal microcirculation, making the diabetic kidney more sensitive to contrast media[21]. DM, one of the major risk factors for the development of cardiovascular events, is an equivalent of CAD and

many patients with CAD have DM or prediabetes[22]. Therefore, the presence of DM as a comorbidity in patients with CAD, for whom radiocontrast-based imaging is frequently required, significantly increases the incidence of CIN. This, in turn, contributes not only to higher mortality and morbidity rates, but also to a considerable economic burden[15]. For this reason, it is important to better understand the mechanisms that predispose the development of CIN and to control them in DM patients, as well as to identify determinants with high predictive values in the prevention of CIN in this susceptible group.

C-peptide and HbA1c are two important molecules that are used in the diagnosis, treatment and follow-up processes of DM patients and act as a kind of biomarker[23]. C-peptide is a reliable marker of endogenous insulin secretion, produced in the same amounts as insulin. It is used in clinical practice to determine treatment modalities in DM patients[24]. C-peptide, which was thought to be an inactive molecule, has been found to be a bioactive molecule in recent studies[25,26]. In many clinical and experimental studies, it has been determined that C-peptide has a positive effect on renal physiology and a renoprotective effect in diabetic nephropathy[27]. Many mechanisms have been implicated in this effect. C-peptide has been shown to bind to certain cellular membranes, such as those of endothelial cells, pancreatic beta cells, renal tubular cells and fibroblasts, where it activates several intracellular signaling pathways through a specific G-protein-coupled receptor[28]. By modulating Nf-κb activity in diabetic nephropathy (DN), it reduces mediators such as TNF-α, TGF-β, Bcl2 and ICAM-1, which play an important role in the pathogenesis of DM[29]. C-peptide has been shown to protect endothelial cells against DM-induced apoptosis[30]. Further evidence has shown that C-peptide exerts potent vasoprotective effects on the renal vasculature network, leading to improved renal function[31]. It has also been found to reduce inflammatory kidney failure by reducing inflammatory mediators such as P-selectin, ICAM-1, interleukins and VCAM-1[32] and to protect diabetic kidney tissues against oxidative damage[33]. All these studies suggest that C-peptide is a powerful kidney protector. Although the curative properties of C-peptide application in acute renal failure have been demonstrated in 2 experimental studies, its effect on contrast medium-mediated acute kidney injury was not known until now[34]. Therefore, we postulate that C-peptide may exhibit renoprotective properties against the development of CIN. However, HbA1c in DM patients exhibits the opposite characteristics[35]. In line with this, one study reported that high HbA1c levels may be an independent predictor for the development of CIN[14]. Therefore, we postulated that combining C-peptide and HbA1c into a single ratio (CHR) might provide a higher predictive value for CIN than evaluating them individually. In this study, we analyzed C-peptide, HbA1c and CHR separately to assess their independent predictive power for CIN in both diabetic and non-diabetic individuals. Although the association was statistically stronger in diabetic patients, our findings suggest that CHR may predict the development of CIN more sensitively than C-peptide or HbA1c alone in all patient groups.

In a study conducted with a small group of patients, patients who developed CIN were associated with higher rates of RRT [13%] and higher ICU mortality (52%)[36]. In our study, this rate was 6.0% for RRT requirement and 49.1% for ICU mortality. Although the mortality rates of the aforementioned study were similar to ours, the need for RRT was lower in our study. This difference may be due to the demographic and clinical differences of the patients or sample size. In our study, DM patients and those with CKD had a higher need for RRT and the incidence of progression to end-stage kidney failure was higher. This finding is consistent with the literature[37]. In our study, CKD and CHR levels were determined as independent predictors for RRT need. The CHR level was lower in patients who needed permanent dialysis than in those who did not. This shows that the balance between the renoprotective effects of C-peptide and the renal adverse effects of HbA1c may be important biomarkers both in the development of CIN and in the subsequent progression of renal failure. Combining and using the balance between both opposing biomarkers in a single fraction can be a useful biomarker tool to be used to take more intensive measures against conditions that predispose to the development of CIN (such as DM, CKD).

Consistent with the literature, the incidence of CIN was higher in STEMI patients, but it was not a risk factor for the need for RRT[38]. Interestingly, unlike in the literature, patients with low baseline creatinine

had a higher risk of developing CIN. This may be because in very small increases in low baseline creatinine values, the proportional increase limit of 25% can easily be reached. For example, a 0.1 mg/dL increase in creatinine does not correspond to the same percentage change in two patients: one with a pre-procedural creatinine of 0.4 mg/dL and another with a pre-procedural value of 0.5 mg/dL. So, in our opinion, the definition of classic CIN cannot adequately cover the patient group with very low initial creatinine levels[39]. Perhaps it would be more appropriate to use the 33% reduction in creatinine clearance, as used by Cely et al., instead of the classical definition (25% increase in serum creatinine within 72 hours)[40].

Limitations

The first limitation is the fact that our study was a single-center study and included a relatively small patient sample. Secondly, differences in illness duration and drug use of DM patients were not recorded, and only Type 2 DM patients were included in the study, which may affect the results. Also, a 90-day total mortality follow-up was only performed for patients who developed CIN. Finally, there may be other parameters affecting the results in these patient groups at risk of multiple comorbidities.

Conclusion

Our study showed that the use of C-peptide, whose renoprotective properties have been clearly demonstrated, and HbA1c, whose renal side effects are already known, in a single fraction is better than considering them separately in predicting the development of CIN and the requirement for RRT. In addition, our study showed that CHR in patients undergoing CAG can be a useful biomarker that can be used in all patient groups, especially in diabetic patients, for predicting the development of CIN and the requirement for RRT. Therefore, implementing more intensive preventive measures in these high-risk patient groups may significantly reduce mortality and morbidity associated with CIN, as well as the resulting economic burden.

Statement of Ethics

All procedures performed in this study involving human participants complied with the ethical standards of the institutional research committee and the Declaration of Helsinki.

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Sažetak

NOVI BIOMARKER ZA PREDVIĐANJE NEFROPATIJE IZAZVANE KONTRASTOM I POTREBE ZA BUBREŽNOM NADOMJESNOM TERAPIJOM U BOLESNIKA PODVRGNUTIH KORONARNOJ ANGIOGRAFIJI: OMJER C-PEPTIDA I HBA1C

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Nefropatija izazvana kontrastom (CIN) glavni je uzrok mortaliteta i morbiditeta s rastućom incidencijom nakon koronarne angiografije (CAG). Iz tog razloga važno je unaprijed identificirati bolesnike koji su skloni CIN-u i sukladno tome poduzeti intenzivne mjere zaštite. U ovom smo istraživanju željeli otkriti ulogu C-peptida, HbA1c i omjera C-peptid/HbA1c (CHR) u predviđanju razvoja CIN-a i potrebe za bubrežnom nadomjesnom terapijom (RRT) u bolesnika koji su podvrgnuti CAG-u. Ukupno 2271 pacijent podvrgnut CAG-u između siječnja 2019. i lipnja 2021. uključen je u ovu prospektivnu opservacijsku studiju. Razine C-peptida i HbA1c izmjerene su svim pacijentima koji su bili podvrgnuti CAG-u, bez obzira na to jesu li dijabetičari ili ne. Pokušali smo identificirati neovisne prediktore za razvoj CIN-a. Osim toga, pacijenti kojima je bila potrebna nadomjesna terapija nakon CIN-a praćeni su u prosjeku 90 dana. U multivarijatnoj analizi CHR je određen kao neovisni prediktor CIN-a i identificiran kao neovisni čimbenik rizika za potrebu za RRT-om u bolesnika koji su podvrgnuti CAG-u. Glavno otkriće naše studije jest da je CHR neovisni prediktor za razvoj CIN-a i potrebu za RRT-om u bolesnika koji su podvrgnuti CAG-u.

Ključne riječi: *Nefropatija izazvana kontrastom; Koronarna angiografija; C-peptid; HbA1c; Nadomjesna bubrežna terapija*